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REVIEW

Cutaneous Mycobacterial Infections

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SUMMARY Humans encounter mycobacterial species due to their ubiquity in different environmental niches. In many individuals, pathogenic mycobacterial species may breach our first-line barrier defenses of the innate immune system and modulate the activation of phagocytes to cause disease of the respiratory tract or the skin and soft tissues, sometimes resulting in disseminated infection. Cutaneous mycobacterial infections may cause a wide range of clinical manifestations, which are divided into four main disease categories: (i) cutaneous manifestations of *Mycobacterium tuberculosis* infection, (ii) Buruli ulcer caused by *Mycobacterium ulcerans* and other related slowly growing mycobacteria, (iii) leprosy caused by *Mycobacterium leprae* and *Mycobacterium lepromatosis*, and (iv) cutaneous infections caused by rapidly growing mycobacteria. Clinically, cutaneous mycobacterial infections present with widely different clinical presentations, including cellulitis, nonhealing ulcers, subacute or chronic nodular lesions, abscesses, superficial lymphadenitis, verrucous lesions, and other types of findings. Mycobacterial infections of the skin and subcutaneous tissue are associated with important stigma, deformity, and disability. Geography-based environmental exposures influence the epidemiology of cutaneous mycobacterial infections. Cutaneous tuberculosis exhibits different clinical phenotypes acquired through different routes, including via extrinsic inoculation of the tuberculous bacilli and dis-

Citation Franco-Paredes C, Marcos LA, Henao-Martínez AF, Rodríguez-Morales AJ, Villamil-Gómez WE, Gotuzzo E, Bonifaz A. 2019. Cutaneous mycobacterial infections. Clin Microbiol Rev 32:e00069-18. https://doi.org/10.1128/CMR.00069-18.

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Published 14 November 2018

semination to the skin from other sites, or represents hypersensitivity reactions to *M. tuberculosis* infection. In many settings, leprosy remains an important cause of neurological impairment, deformity, limb loss, and stigma. *Mycobacterium lepromatosis*, a mycobacterial species related to *M. leprae*, is linked to diffuse lepromatous leprosy of Lucio and Latapí. *Mycobacterium ulcerans* produces a mycolactone toxin that leads to subcutaneous tissue destruction and immunosuppression, resulting in deep ulcerations that often produce substantial disfigurement and disability. *Mycobacterium marinum*, a close relative of *M. ulcerans*, is an important cause of cutaneous sporotrichoid nodular lymphangitic lesions. Among patients with advanced immunosuppression, *Mycobacterium kansasii*, the *Mycobacterium avium-intracellulare* complex, and *Mycobacterium haemophilum* may cause cutaneous or disseminated disease. Rapidly growing mycobacteria, including the *Mycobacterium abscessus* group, *Mycobacterium chelonei*, and *Mycobacterium fortuitum*, are increasingly recognized pathogens in cutaneous infections associated particularly with plastic surgery and cosmetic procedures. Skin biopsies of cutaneous lesions to identify acid-fast staining bacilli and cultures represent the cornerstone of diagnosis. Additionally, histopathological evaluation of skin biopsy specimens may be useful in identifying leprosy, Buruli ulcer, and cutaneous tuberculosis. Molecular assays are useful in some cases. The treatment for cutaneous mycobacterial infections depends on the specific pathogen and therefore requires a careful consideration of antimicrobial choices based on official treatment guidelines.

KEYWORDS Buruli ulcer, *Mycobacterium*, *Mycobacterium kansasii*, *Mycobacterium marinum*, *Mycobacterium ulcerans*, cutaneous, leprosy, mycobacteria, nontuberculous mycobacteria, tuberculosis

INTRODUCTION

Human Societies and the Origin and Spread of Major Mycobacterial Pathogens

Mycobacteria are aerobic rod-shaped bacteria that do not form spores and that are lipid rich with long-chain mycolic acids in their cell walls, which are largely responsible for their acid fastness (1). Modern genomic, phylogenetic, and ecological studies have shed light on the origins of most important mycobacterial infections affecting humans (1–20). For example, leprosy and tuberculosis (TB) have had a profound effect on human suffering for thousands of years (16). Modern molecular genomic analysis of ancient human remains and records of ancient texts demonstrate that the spread of some mycobacterial diseases, including TB and leprosy, track historical milestones of human societies (7–10). These events include waves of human expeditionary, military, or commercial migrations (8). Phylogeographic studies uncovered the origin of leprosy in eastern Africa and its spread through the Silk Road or the transatlantic slave migration trade routes (7, 8, 10, 12). The domestication of animals and the development of water distribution systems also influenced the transmission dynamics of mycobacterial infections (16). Similarly, phylogeographic studies of the tuberculous bacilli have shown that the dominant clone of smooth tubercle bacilli (*Mycobacterium canettii*) emerged in eastern Africa and later diversified into the *Mycobacterium tuberculosis* complex during the worldwide spread of TB by waves of human migration (5, 11).

Mycobacterial Species as Human Pathogens

The genus *Mycobacterium* is part of the order *Actinomycetales* and the phylum *Actinobacteria* and belongs to a variety of environmental habitats, including natural waters, soils, and drinking water distribution systems (1, 20–23). Mycobacterial species reside in a wide-variety of environments due to multiple adaptations. Some of the features include the presence of a lipid-rich hydrophobic outer membrane, which is a major determinant of surface adherence, biofilm formation, aerosolization, and antibiotic/disinfectant resistance. Additionally, mycobacteria have the ability to replicate at a low rate, providing them with a decreased susceptibility to most antimicrobial agents,

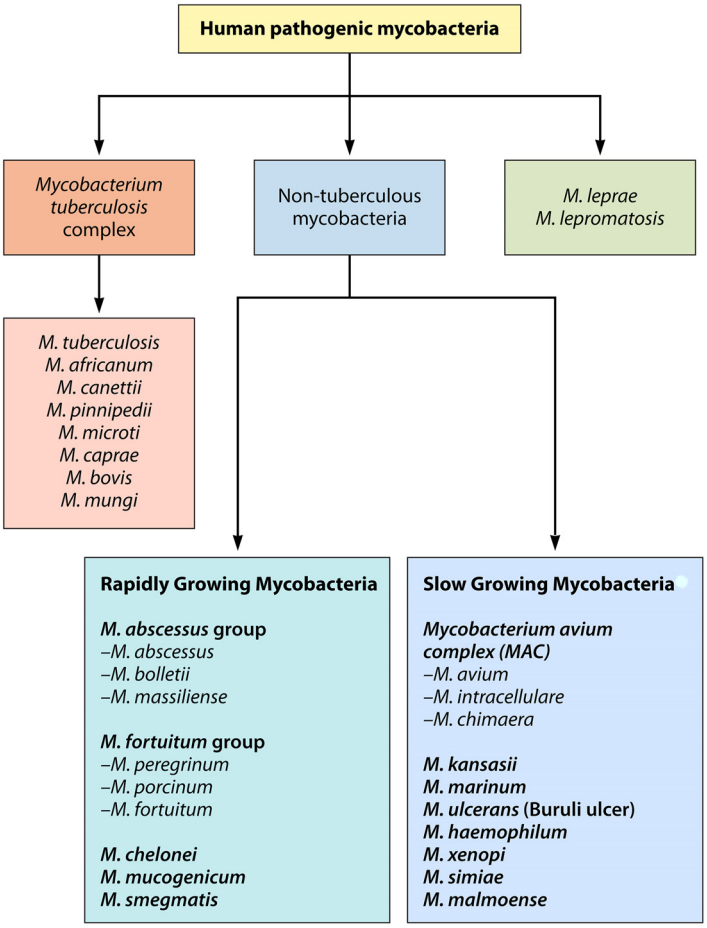

FIG 1 Classification of major pathogenic mycobacteria.

and they also possess the ability to grow at low carbon levels, thus making them effective competitors in low-nutrient environments (oligotrophs) (21, 22).

From a large mycobacterial pool, some species have evolved into potential major human pathogens (20, 23–25) (Fig. 1). Genomic events such as genome reduction, critical gene acquisition, gene transfer, mutations, and recombination permitted environmental mycobacteria to evolve into host-associated pathogens (2, 5, 9, 11, 14–16, 19). Phylogenetic reconstructions of genomic sequences suggest that *Mycobacterium marinum*, *Mycobacterium leprae*, *Mycobacterium ulcerans*, and *M. tuberculosis* evolved from a common environmental ancestor (2, 15, 16, 19). Their gene loss or acquisition reflects fluctuating environmental challenges and host-specific pathoadaptations (2, 3, 5) (Table 1). The molecular mechanisms by which *M. tuberculosis* and *M. leprae* have evolved to cause disease involved complex interactions between the pathogen and the host. In contrast, the pathogenicity of *M. ulcerans* derives from the acquisition of a plasmid encoding the polyketide toxin mycolactone (2, 5).

Mycobacterial species are present in the environment in water and soil niches that are shared with humans (19, 21, 22). In the human host, mycobacterial infections may affect many anatomical sites, but since they enter through the skin and mucosal barriers, they lead mostly to pulmonary or cutaneous infections (25–28). The pathogenesis of cutaneous mycobacterial infections is the result of hematogenous dissemination, local or regional spread from a deep-seated infection, or direct inoculation into the skin and soft tissues (24). The modes of transmission of the different mycobacterial species involved in cutaneous disease include zoonotic transmission (e.g., foodborne transmission of *Mycobacterium bovis* by ingestion of unpasteurized dairy products) (16,

TABLE 1 Comparison of epidemiological and clinical features of the four categories of cutaneous mycobacterial infections: cutaneous tuberculosis, leprosy, Buruli ulcer, and disease caused by nontuberculous mycobacteria

Parameter	Cutaneous tuberculosis	Leprosy	Buruli ulcer	Disease caused by NTM	
				Rapidly growing	Slowly growing[a]
Mycobacterial species	*M. tuberculosis*, *M. bovis*, bacillus Calmette-Guérin	*M. leprae*, *M. lepromatosis*	*M. ulcerans*	*M. abscessus*, *M. fortuitum*, *M. chelonae*	*M. marinum*, *M. ulcerans*, *M. haemophilum*
Microbiological diagnosis	Culture; clinical diagnosis supported by histopathology and molecular detection methods (PCR)	*M. leprae* and *M. lepromatosis* are noncultivable; clinical diagnosis supported by histopathology and molecular detection methods (PCR)	*M. ulcerans* grows at 29–33°C, colonies are yellowish, rough and distinct from one another; clinical diagnosis supported by histopathology and molecular detection methods (PCR)	*M. abscessus* complex grows within 7 days on Middlebrook 7H10 or 7H11 agar and Bactec 12B; some strains of *M. chelonae* grow at 30°C	*M. haemophilum* requires iron or hemin for growth at 30°C
Genome	Genome of 4.4 Mb with 4,000 genes and only 6 pseudogenes (91% coding capacity); no major reductive evolution	*M. leprae* suffered reductive evolution and large pseudogene (1, 116) formation resulting in the 3.31-Mb genome; only 50% coding capacity by 1,605 genes; *M. lepromatosis* has approximately 13% genomic-scale difference compared to *M. leprae*	*M. marinum and M. ulcerans* share 97% of genes; selected genes facilitate occupying an aerobic niche environment and osmotically stable, dark, and extracellular environments	*M. abscessus* genome is 5 Mb with some homologous genes that determine virulence, similar to *M. tuberculosis*, with some genes acquired via horizontal transfer from *Pseudomonas* and *Burkholderia cepacia*	*M. ulcerans* downsized from 6.6 MB (*M. marinum*) to 5.8-Mb genome associated with lateral gene transfer and reductive evolution; *M. marinum*, *M. ulcerans*, and *M. haemophilum* are phylogenetically closely related and produce similar cutaneous forms of the disease
Target cells of infection	Intracellular: macrophages (alveolar) and in the reticuloendothelial system; nonclassical immune cells (epithelial cells, endothelial cells, fibroblasts, adipocytes, glia, and neurons)	Intracellular: Schwann cells, histiocytes, keratinocytes	Extracellular: extracellular matrix in subcutaneous tissues where *M. ulcerans* directs the production of the polyketide toxin mycolactone, leading to tissue necrosis and local tissue and systemic immunosuppression	Intracellular: histiocytes, macrophages	Intracellular: histiocytes, macrophages
Pathogenic mechanisms	Intracellular persistence in macrophages and histiocytes causes necrotizing granulomas that cause tissue destruction of skin and soft tissues	Infection of Schwann cells leads to peripheral nerve dysfunction secondary to demyelination; reprogramming of Schwann cells is linked to disseminated disease	Destructive ulcerative ulcers (Buruli or Bairnsdale ulcer) with subcutaneous fat necrosis	Granulomatous inflammation with tissue destruction	Granulomatous inflammation with tissue destruction

(Continued on next page)

TABLE 1 (Continued)

Parameter	Cutaneous tuberculosis	Leprosy	Buruli ulcer	Disease caused by NTM	
				Rapidly growing	Slowly growing[a]
Environmental determinants	Members of the *Mycobacterium tuberculosis* complex can be shed by infected hosts to the environment in sputum, feces, and urine by humans, in milk from dairy animals (cattle), and in infected body tissues from other domestic and wild animals; free-living amoebas may act as macrophage-like niches in the environment	Armadillo is a natural host in the Western Hemisphere and causes a zoonosis in the southern US; red squirrel identified as a reservoir in the UK; in some settings some primate species may become reservoirs of *M. leprae*; there is evidence of viable *M. leprae* found in soil, water, and free-living amoebas (*Acanthamoeba* spp.)	*Mycobacterium ulcerans* transmission cycle involves aquatic insect vectors, aquatic plants, and aquatic animals; aquatic plants (e.g., *Rhizoclonium* spp., *Hippeastrum reticulatum*) favor growth of and biofilm production by *M. ulcerans*; there are two different ways that *M. ulcerans* persists in the environment and infects aquatic animals (in the savanna landscape residing in stagnant or slowly moving waters and in tropical rainforests dwelling in alkaline waters, and its growth is dependent on climate changes)	Biofilms in urban water networks; free-living amoebas act as reservoirs	Fish and aquatic environments (biofilms in rocks and coral); free-living amoebas act as reservoirs
Vector transmission	The ancestor of the smooth bacillus *M. canettii* and the ancestor of *M. tuberculosis* complex likely had nonmammalian reservoirs (e.g., plant or insect) prior to the Neolithic revolution	Some mosquitoes (*Culex fatigans* and *Cimex hemipterus* caught in the field in an area of endemicity in India harbor viable *M. leprae*); laboratory-bred *Culex fatigans* and *Cimex hemipterus* are able to take up leprosy bacilli from blood of patients with untreated lepromatous leprosy; the feasibility of biting arthropods amplifying the transmission of leprosy through mechanical studies demonstrated that large numbers of bacilli are readily available to the biting apparatus of arthropods among individuals with untreated multibacillary leprosy; bacteremia in cases of leprosy may make viable bacilli available to biting arthropods	*Naucoridae* (aquatic insects) in West African countries (Ghana, Benin, Togo) harbor *M. ulcerans*	Unknown	Unknown

[a]Slowly growing mycobacteria include a large number of species other than the ones included in this table. Other than the three species included in this table, *M. kansasii* often produces skin and soft tissue involvement.

23), person-to-person transmission (e.g., of leprosy) (29, 30), vector-borne transmission (possibly for *Mycobacterium ulcerans*) (3, 31–33), and acquisition of infection from environmental exposures (e.g., freshwater or salt water injuries leading to *Mycobacterium marinum*, *M. ulcerans*, or *Mycobacterium haemophilum* infection) (24, 33–38) (Table 1). Nontuberculous mycobacteria (NTM), i.e., those mycobacterial species that do not cause tuberculosis or leprosy, are frequently present in municipal water systems, residing mostly in the pipeline biofilms (21, 22, 38, 39). Free-living amoebas, including *Acanthamoeba* or *Vermamoeba*, may act as reservoirs of *M. leprae* and NTM (38–41).

The most common cutaneous forms of acquisition of NTM involve direct inoculation via trauma (33), postsurgical infections (42), or iatrogenic acquisition with indwelling medical devices, plastic surgery, cosmetic procedures, or prosthetic implants (24, 42). Mycobacteria may seed the skin and soft tissues during systemic dissemination in immunosuppressed individuals (24, 25, 37, 42–44). There is some evidence of potential human-to-human transmission of *Mycobacterium abscessus* subsp. *massiliense* among patients with cystic fibrosis (43, 44).

The precise mode of transmission of leprosy remains uncertain but probably involves human-to-human contact through respiratory droplets (29, 30, 45–47) or through blood transfusion (48). Ecological data suggest that environmental factors, such as trauma or skin breaks during soil and water exposures, insect vectors, free-living amoebas, and animal reservoirs (e.g., armadillos, squirrels, felines, or other animals), influence leprosy transmission (39, 47, 49–63). Zoonotic transmission from armadillos acting as reservoirs of infection has been confirmed for autochthonous southeast United States cases (51, 52). Armadillos may also play a role in the transmission of leprosy in some areas in Colombia (55) and in Brazil (56). In some of the British Isles, red squirrels may develop leprosy-like lesions due to either *M. leprae* or *Mycobacterium lepromatosis* (53).

In this review, we group cutaneous mycobacterial infections into four major categories: (i) infection due to *Mycobacterium tuberculosis* complex, (ii) infection caused by *Mycobacterium leprae* and *M. lepromatosis*, (iii) infection caused by *Mycobacterium ulcerans* and other slowly growing mycobacteria (SGM), and (iv) infection due to rapidly growing mycobacteria (RGM).

CUTANEOUS TUBERCULOSIS

Cutaneous forms of tuberculosis are a rare clinical manifestation of *M. tuberculosis* or *M. bovis* infection, comprising approximately only 1 to 2% of all TB cases (47, 64–67). In settings where immunization programs administer the bacillus Calmette-Guérin (BCG) vaccine, an attenuated form of *M. bovis*, cutaneous complications, including local reactions, abscess formation, ulcerations, scrofuloderma, and, rarely, disseminated infections, may occur (64, 65). Visceral tuberculosis (pulmonary or extrapulmonary) is rarely associated with concomitant cutaneous involvement (68). However, when it occurs, it is usually in the form of scrofuloderma or lupus vulgaris (47, 67–70). The ability to culture *M. tuberculosis* facilitates the diagnosis of the cutaneous disease, in contrast to *M. leprae* (47). Therefore, the gold standard for diagnosing cutaneous tuberculosis is mycobacterial culture of skin biopsy specimens or via molecular detection (47, 71). Depending on the BCG vaccination status, tuberculin skin testing using purified protein derivative has a specificity of 63% and a sensitivity between 33 and 96% for cutaneous tuberculosis (47, 72). Interferon gamma (IFN-γ) release assays (IGRAs) demonstrate a sensitivity of 92% and a specificity of 76% in individuals with cutaneous TB (73).

Cutaneous forms of TB are currently classified according to clinical morphological patterns, the route of acquisition (exogenous inoculation, hematogenous spread, or regional extension), and the host immune status (47, 64–66, 71). In both tuberculosis and leprosy, well-organized epithelioid granulomas are associated with a high degree of cell-mediated immunity (CMI) and a reduced bacterial load (47). Histologically, perineural granulomas assist in distinguishing tuberculoid leprosy from cutaneous TB. Cutaneous TB cases associated with increased CMI and few noted bacilli are classified

as high-immune forms (i.e., tuberculosis verrucose cutis, lupus vulgaris, and tuberculids) (47, 69) (Table 2).

Tuberculosis verrucosa cutis represents primary *M. tuberculosis* infection. It occurs predominantly in the extremities and manifests as violaceous or brownish warty plaque-like lesions that present in a previously sensitized host because of direct inoculation of the TB bacillus (47). Lesions consist of usually single painless indurated warty plaques that may potentially ulcerate. This clinical form presents predominantly in children, but when it is present in adults, it tends to occur among those with occupational exposures, such as butchers or farmers. The most frequent sites of involvement include the fingers and dorsum of the hands, followed by ankles or buttocks (Fig. 2) (47, 69). The differential diagnosis of cutaneous TB includes other granulomatous conditions, including sarcoidosis, leprosy, leishmaniasis, fungal conditions (blastomycosis and chromoblastomycosis), Majocchi's granuloma, halogenoderma, squamous cell carcinomas, orf disease (parapox virus), and syphilis (24, 47).

Primary-inoculation TB occurs after exogenous inoculation in individuals not previously sensitized to *M. tuberculosis*, and it represents a phenomenon analogous to the Ghon complex in the lung (47, 69). An initial nodular or papular lesion frequently identified in the extremities or in the face evolves into a shallow ulcer with associated regional lymphadenopathy (67, 69, 71). Some identified risk factors for developing this clinical variant include minor trauma, tattoos, piercing, and surgical procedures with unsterilized equipment (47, 71). Untreated primary-inoculation TB may resolve in a period of 12 months or longer or may progress to disseminated forms of the disease by hematogenous spread of the bacillus to other organs. Some patients may have associated erythema nodosum. Other diseases that need to be considered in the differential diagnosis include bartonellosis, tularemia, leishmaniasis, syphilis, eumycetoma, and yaws (47, 69).

Scrofuloderma is a form of TB that is caused by *M. tuberculosis* or *M. bovis* and commonly affects children, adolescents, and older adults (47, 69). This variant of TB is the result of contiguous spread to the overlying skin from adjacent structures such as a lymph node, joint, bone, or the epididymis. When *M. bovis* infection manifests as scrofuloderma, it is often the result of consumption of unpasteurized milk (47, 69, 71). The most common sites of involvement are the neck, axillae, or groin (Fig. 3). Scrofuloderma initially presents as a firm subcutaneous nodule or nodules that gradually enlarge, become confluent, ulcerate, and form draining sinus tracts of purulent or caseous material. These lesions eventually lead to significant scarring (47, 69). Scrofuloderma may be associated with concomitant pulmonary tuberculosis, particularly when it is associated with right supraclavicular and cervical lymphadenitis (47, 66, 67, 69). Scrofuloderma needs to be distinguished from infections caused by nontuberculous mycobacteria (i.e., *Mycobacterium avium-intracellulare* complex [MAC], *M. haemophilum*, or *Mycobacterium scrofulaceum*), hidradenitis suppurativa, actinomycosis, and eumycetoma (47, 66, 69).

Tuberculosis cutis orificialis occurs among severely immunocompromised middle-aged and older adults with advanced pulmonary, gastrointestinal, or genitourinary tuberculosis (47). This rare type of cutaneous TB occurs on the nasal, oral, or anogenital skin or mucosa and is clinically important to consider in individuals with periorificial nonhealing ulcers. The lesions originate from autoinoculation of the mucosal orifices by other cutaneous draining sites from internal organ infections. The differential diagnosis of this condition includes paracoccidioidomycosis, syphilis, lymphogranuloma venereum, pyoderma gangrenosum, and skin malignancies (47, 69).

Lupus vulgaris is a chronic form of cutaneous TB that may occur due to regional lymphatic or hematogenous spread in individuals with reinfection or reactivation of latent TB infection or BCG vaccination (47, 69, 71). Lupus vulgaris may occur concomitantly with scrofuloderma, or it rarely may be associated with primary-inoculation TB. Lupus vulgaris occurs predominantly in Asia and southern Africa. This progressive clinical form originates through lymphatic spread or by contiguous spread from a lymph node or bone (47). This clinical form affects women predominantly and mani-

TABLE 2 Modes of acquisition, history of previous sensitization to *Mycobacterium tuberculosis*, and clinical features of the cutaneous presentations of tuberculosis

Clinical presentation	Mode of acquisition	Bacillary load[a]	Previous sensitization to *M. tuberculosis*[b]	Clinical features
Tuberculosis verrucosa cutis	Exogenous inoculation	Paucibacillary	++	Verrucous lesions in dorsum of hands or digits, ankles, or buttocks
Primary inoculation tuberculosis	Exogenous inoculation	Multibacillary	−	Nodular lesion in the face or in the upper or lower extremities with associated lymphadenopathy
Scrofuloderma	Contiguous extension	Multibacillary	+	More common in children, adolescents, and the elderly; most common site is the neck; may coexist with pulmonary TB
Lupus vulgaris	Contiguous extension or hematogenous spread	Paucibacillary	++	Affects women predominantly and manifests as smoldering nodules, annular plaques, or hypertrophic or vegetative lesions; initial lesions start as a collection of reddish papules that coalesce to form plaques with serpiginous or verrucous borders with central clearing and atrophy
Tuberculosis cutis orificialis	Contiguous extension	Multibacillary	−	Periorificial nonhealing ulcers of the nasal, oral, or anogenital skin or mucosa among individuals with advanced forms of pulmonary, gastrointestinal, or genitourinary TB
Acute miliary tuberculosis	Hematogenous spread	Multibacillary	−	Immunocompromised individuals, may present with single or multiple subcutaneous nodules that may potentially evolve into ulcers or draining sinuses without regional adenopathy
Metastatic tuberculosis abscess	Hematogenous spread	Multibacillary	−	May appear as a cellulitis or as purpuric papules that may umbilicate and become crusted among individuals with severe immunosuppression (i.e., AIDS or severe malnutrition)
Tuberculids[c]	Hypersensitivity reactions to *M. tuberculosis* infection	Negative cultures and stains of affected lesions[d]	+++	Erythema induratum of Bazin (more common in females) and presents as granulomatous lobular painful panniculitis, usually in the lower extremities; papulonecrotic tuberculid (more common in children and young adults), may present with lupus vulgaris and scrofuloderma, presents with dark red or violaceous papules that evolve to pustules or become necrotic, fever and constitutional symptoms present; Lichen scrofulosorum (more common in children and young adults) with lymphatic or pulmonary TB (this condition has also been associated with BCG vaccination and with *M. avium-intracellulare* infection

[a]The bacillary load correlates with the degree of cell-mediated immune response (CMI). High immunity determines the occurrence of tuberculosis verrucose cutis, lupus vulgaris, and all forms of the tuberculids. Low immunity against *M. tuberculosis* is a risk factor for tuberculosis cutis orificialis, acute military tuberculosis, and metastatic tuberculous abscess.

[b]A plus sign indicates a previous history of sensitization to *M. tuberculosis*. A stronger history of sensitization is indicated with two or three plus signs. A minus sign indicates the absence of a previous history of sensitization to *M. tuberculosis*.

[c]The diagnosis of tuberculids is supported by a strongly positive tuberculin skin test or a positive IFN-γ release assay, indicating history of exposure to the tuberculous bacilli, with absence of *M. tuberculosis* in stains or cultures of skin biopsy specimens but evidence of granulomatous inflammation. The response to antituberculosis therapy is also important in confirming these conditions.

[d]*M. tuberculosis* DNA may be detected in some cases of erythema induratum and papulonecrotic tuberculid.

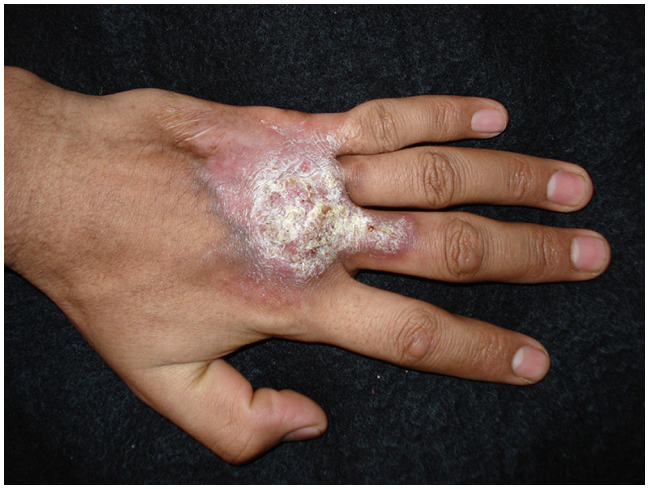

FIG 2 Tuberculosis verrucosa cutis of the hand, manifesting as verrucous plaques caused by direct inoculation of the tuberculous bacilli into the skin of an individual previously sensitized to this pathogen.

fests as smoldering nodules and annular plaques, or it may present with hypertrophic or vegetative lesions. Sometimes it may start as a collection of reddish papules that coalesce to form plaques with serpiginous or verrucous borders with central clearing and atrophy. The sites most frequently affected include the lower extremities or buttocks in tropical and subtropical settings, whereas in temperate areas lesions occur most frequently in the head and neck. Lesions of lupus vulgaris may have the appearance of "apple jelly" on diascopy (47, 69, 71). The differential diagnosis of lupus vulgaris is with conditions such as discoid lupus, sarcoidosis, Spitz nevus, chromoblastomycosis, tuberculoid leprosy, and leishmaniasis. Untreated cases of lupus vulgaris may evolve into verrucous squamous cell carcinoma (67, 69).

Hematogenous metastatic tuberculous abscesses occur among immunocompromised individuals and may present with single or multiple subcutaneous nodules that may potentially evolve into ulcers or draining sinuses without regional adenopathy (47, 69). Some lesions may mimic scrofuloderma. Similarly, acute military tuberculosis represents primary infection in individuals with advanced immunosuppression, includ-

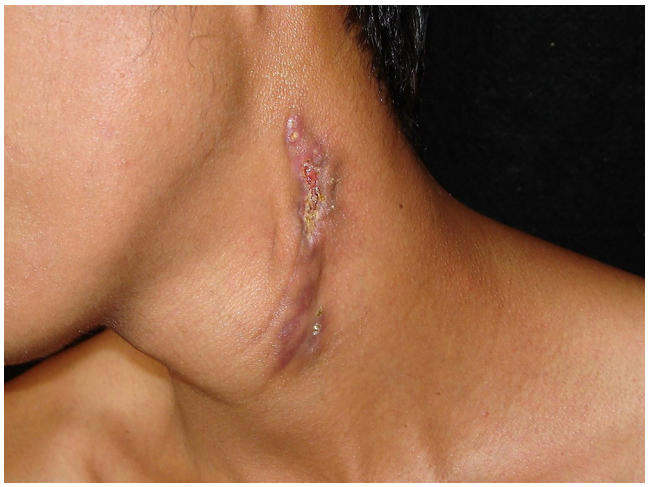

FIG 3 Scrofuloderma presenting in the neck, resulting from direct extension of an infected left cervical lymph node into the overlying cutaneous structures. This form is also known as tuberculosis colliquative cutis. This form of cutaneous tuberculosis is also associated with infection caused by *Mycobacterium bovis* or bacillus Calmette-Guérin.

ing those with HIV infection/AIDS (71). This clinical form may appear as a cellulitis or as purpuric papules that may become umbilicated and crusted (49).

Tuberculids are cutaneous disorders that represent hypersensitivity reactions to mycobacterial antigens. The most frequent tuberculid is erythema induratum of Bazin, but some individuals may manifest lichen scrofulosorum, or papulonecrotic tuberculid (47, 67, 69) (Table 2).

Treatment of cutaneous TB follows the same recommendations as for other forms of TB, with multidrug therapy (MDT) and ideally adjusted by culture and susceptibility data (47, 67, 69). The management of extensive scrofuloderma sometimes requires surgical intervention. Reconstructive surgery may be indicated for severe forms of cutaneous TB such as lupus vulgaris (69, 71).

LEPROSY

Leprosy is a mycobacterial infection caused by *Mycobacterium leprae* that tends to be chronic and to compromise human societies by producing peripheral nerve damage, limb loss, blindness, and disfiguring skin lesions (4, 72, 74). Leprosy occupies a prominent position among infectious diseases due to its high frequency of disability and associated stigma (75–78).

M. leprae is a noncultivable obligate intracellular pathogen with a slow division time that targets peripheral nerves by predominantly infecting Schwann cells and histiocytes and keratinocytes in the skin (72, 74, 78–90). The entry of the *M. leprae* bacillus into the Schwann cell activates the cell to enter into a dedifferentiation process. The infection may then be carried to other sites by immature cells (83, 84). Innate immune responses by macrophages in human tissues are responsible for initiating nerve damage in leprosy by interaction with phenolic glycolipid 1 (PGL-1) with myelinating glia (88, 89).

The clinical manifestations of leprosy are related to the immune response to the leprosy bacillus (Table 3) (4, 47, 72, 74, 78). The Ridley-Jopling staging system divides leprosy into tuberculoid, borderline (borderline tuberculoid, borderline borderline, and borderline lepromatous), and lepromatous forms (Fig. 4) (72, 74, 78). Leprosy reactions, due to their potential inflammatory compromise of the nerve fibers, lead to sensory and motor loss (85, 90–92). Histologically, intraneural or perineural granulomas may assist the pathologist in distinguishing leprosy from cutaneous tuberculosis (47).

Since the early 1980s, multidrug therapy (MDT) has been universally instituted through active case finding in highly affected communities. This strategy has helped to reduce the prevalence of this infection (93–97). Nevertheless, since 2005, the number of reported new cases has remained consistently stable despite continued use of multidrug therapy (4, 93, 95). The number of new cases will reach the 4 million mark by 2020 (since 2000) (76). Many of these new patients already have grade 2 neurological disability by the time of their diagnosis (96, 97). Since cases of leprosy in children indicate ongoing transmission of *M. leprae* in settings of endemicity, targeted screening involving school-based surveillance followed by continuous household surveillance increases early detection of new leprosy cases (97). Molecular detection methods and phenolic glycolipid 1 (PGL-1) serological data in combination with spatial epidemiology increase detection of leprosy cases (98). Early identification of new cases likely prevents further transmission, but, importantly, it may also reduce the risk of neurological dysfunction and disability associated with leprosy (96–98). There are multiple remaining hazards in the epidemiology of leprosy that may make it impossible to eliminate leprosy transmission by the year 2020 (96, 97).

The management of leprosy requires the use of MDT in combination with steroids or other anti-inflammatory drugs among those with leprosy reactions (72, 74, 78). Since *M. leprae* is not cultivable, the bacteriostatic and bactericidal effects of antimycobacterial drugs against *M. leprae* have been assessed in laboratory studies (47). The WHO recommended the institution of multidrug therapy with dapsone, rifampin, and clofazimine in 1982 (47, 97, 99). Relapse or reinfection is considered a rare clinical phenomenon (47, 78, 86, 87). New cutaneous lesions presenting during or after completing MDT are most likely caused by leprosy reactions (47, 85, 91, 92). Among

TABLE 3 Clinical spectrum of leprosy and leprosy reactions (reversal reactions and erythema nodosum leprosum)

Parameter	Ridley-Jopling classification:				
	Tuberculoid	**Borderline tuberculoid[a]**	**Borderline borderline**	**Borderline lepromatous**	**Lepromatous**
Reversal reactions[b]	−	++	++	++	−
Erythema nodosum leprosum[c]	−	−	−	++	++
WHO classification	Paucibacillary	Paucibacillary	Multibacillary	Multibacillary	Multibacillary
Clinical features	Single or very few hypopigmented macules or plaques with a raised edge, dry, scaly, hairless with hypoesthesia or anesthesia; few peripheral nerves are commonly enlarged	Skin lesions (hypopigmented anesthetic patches that become confluent); moderate nerve involvement; may have late neural thickening with asymmetrical anesthesia and paresis	Skin lesions (hypopigmented anesthetic patches with punched-out centers and raised erythematous borders); multiple nerve involvement with symmetrical thickened nerves; asymmetrical anesthesia and paresis may be present	Skin lesions (widely distributed nodules with diffuse skin infiltration); multiple nerve involvement with symmetrical involvement (thickened nerves); symmetrical glove and stocking anesthesia; deformity, amputation, and disability	Widely distributed skin lesions (macules, nodules, erythematous papules); diffuse skin infiltration with thickened peripheral nerves; symmetrical glove-and-stocking anesthesia; deformity, amputation, and disability
Multidrug treatment recommendations					
U.S. National Hansen's Disease Program	Dapsone at 100 mg/day for 12 mo; rifampin at 600 mg/day for 12 mo		Dapsone at 100 mg/day for 24 mo; rifampin at 600 mg/day for 24 mo; clofazimine at 50 mg/day for 24 mo (may substitute daily minocycline)		
WHO	Dapsone at 100 mg/day for 6 mo; rifampin at 600 mg once monthly under supervision for 6 mo		Dapsone at 100 mg/day for 12 mo; rifampin at 600 mg once monthly under supervision for 12 mo; clofazimine at 50 mg/day for 12 mo plus 300 mg every month under supervision for 12 mo		

[a]Borderline forms represent a mixture of signs and symptoms of polar forms.

[b]Management of reversal reaction (type 1 reaction) requires prednisone or prednisolone (40 to 80 mg daily tapered over a 12- to 20-week period.

[c]Treatment of erythema nodosum leprosum (type 2 reaction) involves the use of prednisone or prednisolone (40 to 80 mg daily tapered over a 12- to 24-week period) but sometimes requires a longer taper. Thalidomide at a dose of 200 to 400 mg in divided doses is sometimes used in combination with corticosteroids to control severe erythema nodosum leprosum. Clofazimine may be used in those intolerant to corticosteroids or in combination.

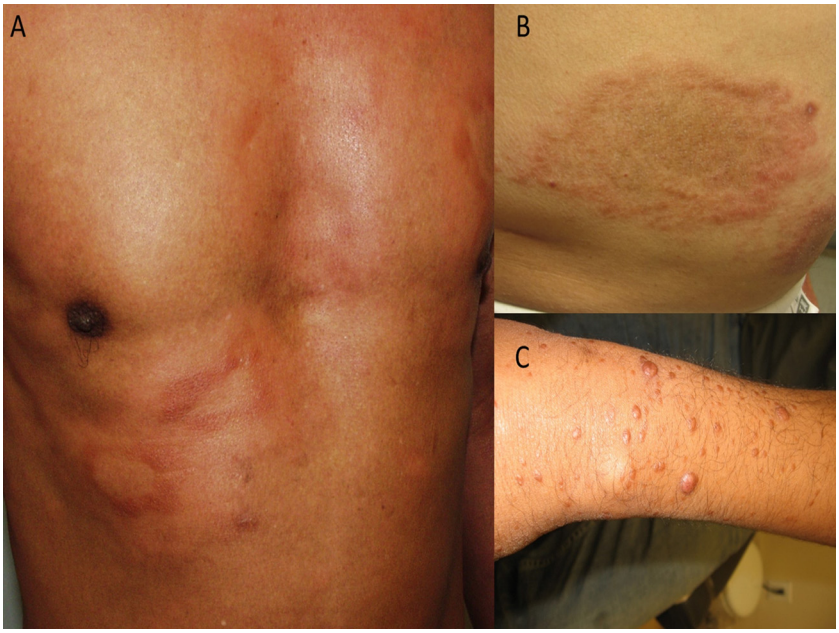

FIG 4 Clinical manifestations of leprosy: borderline tuberculoid (BT) (A), borderline borderline (BB) (B), and lepromatous (LL) (C).

patients with relapse, some researchers have detected drug resistance with the use of rapid DNA-based molecular assays (99).

Diffuse Lepromatous Leprosy of Lucio and Latapí

Mycobacterium lepromatosis was the cause of leprosy in two patients of Mexican origin who died of diffuse lepromatous leprosy (DLL) (100). This form of leprosy is associated with a large bacillary burden that often affects many organs and endothelial cells in subcutaneous tissues, producing dermal vascular occlusion with associated skin necrosis and ulceration (100–105). Infection caused by *M. lepromatosis* is responsible for this unique clinicopathological presentation, which is known as Lucio's phenomenon (101, 102, 104, 106–108). Originally described in Mexico, this clinical form of leprosy also occurs in other countries (102–104). Comparative genomic analyses have demonstrated that *M. lepromatosis* and *M. leprae* are related mycobacterial species that are distinguishable at the genomic level but cause similar clinical manifestations (104–107). There is also some evidence suggesting that *M. lepromatosis* may be associated with severe leprosy reactions, but this association requires further confirmation (103, 107). Clinical studies need to determine whether differences between infection with *M. leprae* and *M. lepromatosis* are clinically distinguishable (102, 107, 108) or whether coinfection with *M. leprae* and *M. lepromatosis* may potentially predispose individuals to experience more severe leprosy reactions (108). In England, Ireland, and Scotland, red squirrels may be infected and develop leprosy-like lesions due to *M. lepromatosis* (53). This strain of *M. lepromatosis* appears to have diverged from the two human strains from Mexico (53).

BURULI ULCER

In 1947, *Mycobacterium ulcerans* was identified as the cause of Buruli ulcer (BU) (2, 3, 31, 32, 109–111). The first cases of BU (formerly known as Bairnsdale ulcer) were identified in Australia in the 1930s (110). BU is considered a neglected tropical disease (NTD) because most cases occur among impoverished populations, often causing an important disability burden (2, 15, 31, 32, 109). *M. ulcerans* and all mycolactone-producing mycobacterial species evolved from *M. marinum* and have become specialized variants living in restricted environments (2, 3). Currently, most cases of Buruli ulcer

occur in parts of western and central Africa, but cases occur in at least 33 countries, mostly in South America and Western Pacific regions (110). WHO identifies approximately 3,000 to 5,000 cases annually, affecting predominantly children less than 15 years of age (20, 31, 32, 109). From an ecological standpoint, BU is a mycobacterial disease identified in rural areas with wetlands, such as ponds, swamps, marshes, impoundments, backwaters, slow-moving rivers, and flooding areas (31, 32). The precise mode of transmission remains to be elucidated, but *M. ulcerans* living in contaminated water can enter the host through insect bites, puncturing injuries, or skin trauma (31, 33). A similar mechanism of transmission maybe responsible for some cases of leprosy (33).

Clinically, BU affects predominantly the lower extremities (>55%) and less often the upper extremities or other body parts (31, 109, 111, 112) The toxin (polyketide), mycolactone secreted by *M. ulcerans* causes tissue destruction (111, 113), local immunosuppression through the inhibition of protein translocation into the endoplasmic reticulum of cytokines of the innate immune system, membrane receptors, adhesion molecules, and T-cell-dependent cytokines (114). Additionally, this toxin induces hypoesthesia by altering the signaling pathways of the type 2 angiotensin II receptors, leading to hyperpolarization of neurons (115). Untreated cases or those with extensive and deep ulcerations develop scarring contractures, deformity, osteonecrosis, and limb loss (31, 109). Other environmental mycobacteria can produce the lipid toxin mycolactone (111, 113). Collectively, these bacteria constitute the group of mycolactone producers, including *Mycobacterium shinshuense* (identified in human cases in Japan), *Mycobacterium pseudoshottsii* (found in striped bass in the United States), *M. marinum* DL240490 (found in European sea bass in the Red Sea), and others (111, 113). All of these species have been isolated from humans, frogs, and fish. They share phenotypic and genotypic features, including the large virulence plasmid (pMUM) required for mycolactone production. Based on these similarities, researchers have proposed recognizing all these bacteria as *M. ulcerans* (31, 32, 111, 113). In fact, there is less than 1% nucleotide variation among all mycolactone-producing mycobacteria (113).

M. ulcerans is a slowly growing environmental mycobacterium causing infection that is considered to have an incubation period of 5 to 8 weeks, but this may be as long as six months in areas of endemicity (31, 109). BU often presents as a painless nodule, as a large indurated plaque, or as diffuse painless swelling of the lower extremities, upper extremities, or face (109). In a period of approximately 4 weeks, the nodule, plaque, or edematous area evolves into an ulcer with undermined borders. The diagnosis of Buruli ulcer is mostly a clinical one and is based on the age of presentation, geographic area, and location (31, 109, 112). The most important conditions that should be considered in the differential diagnosis of BU include tropical phagedenic ulcers, cutaneous tuberculosis, vascular (venous or arterial) ulcerations, diabetic foot ulcerations, pyoderma gangrenosum, infections due to *Haemophilus ducreyi*, cutaneous leishmaniasis, ulcerative yaws, fungal infections (e.g., chromoblastomycosis), and pyogenic ulcerations (e.g., caused by *Staphylococcus aureus*) (24, 109, 112). The diagnosis of BU maybe confirmed by direct microscopy of suspicious lesions, histopathology of skin biopsy specimens, culture, and IS*2404* PCR (PCR) (24, 31, 109). Rapid diagnostic tests to detect mycolactone are currently under evaluation for use as point-of-care tests in areas of high endemicity (109). The histopathology of BU demonstrates large numbers of extracellular bacilli during the acute phase of infection (24, 47, 109).

For clinical staging purposes, BU is divided into three categories by the degree of cutaneous involvement. Category I is a single small lesion. Category II is defined by the presence of nonulcerative or ulcerative plaques and edematous forms (Fig. 5). Category III is when there is evidence of severe disease with dissemination, osteitis, osteomyelitis, or joint involvement (31, 109). Early diagnosis and treatment are crucial to minimize morbidity and prevent long-term disability (2, 3, 109). However, in most countries, at least 70% of all cases are diagnosed in the stage with deep ulceration. HIV coinfection/AIDS appears to foster the rapid progression of lesions into severe ulcerative stages (31, 109).

FIG 5 An 11-year-old male demonstrating a destructive panniculitis causing ulceration with undermined borders, characteristic of Buruli ulcer.

Treatment of BU consists of a combination of antimycobacterial drugs and wound management interventions (109, 112). Surgical debridement and skin grafting are used to speed wound healing in those with large lesions. Antimicrobial regimens of 8 weeks or longer are recommended, irrespective of the clinical staging, and include a combination of rifampin and streptomycin (31, 109). Alternatively, a combination of rifampin and clarithromycin or rifampin and moxifloxacin could be used (109, 112).

NONTUBERCULOUS MYCOBACTERIA

The NTM group constitutes mycobacterial species other than those belonging to the *M. tuberculosis* complex and that do not cause leprosy (1, 42). Historically, NTM were classified according to the Runyon classification based on their growth rates and their ability to produce pigment in response to light (1, 115). Currently, the NTM group is also divided into two major subgroups defined by their ability to grow on solid culture media: (i) rapidly growing mycobacteria (RGM) and (ii) slowly growing mycobacteria (SGM) (Fig. 1) (1). Infections due to NTM can produce pulmonary or extrapulmonary disease in immunocompromised hosts (1, 24, 42).

Recent studies have demonstrated that the prevalence of nontuberculous mycobacterial infections is increasing in many settings (24–28). The clinical spectrum of disease associated with mycobacterial pathogens depends on the route of exposure and host susceptibility factors (25–27). Pulmonary nontuberculous mycobacterial infections are multisystem and multigenic diseases (26). Affected individuals tend to have more frequent protein variants in immune, cystic fibrosis transmembrane conductor regulator (CFTR), and connective tissue genes (26, 27). However, those suffering from cutaneous involvement of NTM usually possess other risk factors (Table 4) (24). Disseminated NTM infections affect severely immunocompromised human hosts, including those with primary immunodeficiencies, such as genetic or acquired defects of the IFN-γ–interleukin-12 (IL-12) pathway (e.g., GATA2 deficiency or anti-IFN-γ autoantibodies), or acquired immunodeficiencies, such as HIV infection/AIDS, transplant-associated immunosuppression, and treatment with biological agents such as anti-tumor necrosis factor alpha (anti-TNF-α) receptor blockers (26, 27, 116).

Rapidly Growing Mycobacteria

Cutaneous NTM infections are transmitted via direct inoculation through skin barrier breaks, which may occur during trauma, surgical procedures, plastic surgery (including liposuction), injections, tattoos, acupuncture, and body piercings (Table 4) (1, 24, 42, 117). Cosmetic procedures such as mesotherapy (multiple injections of pharmaceutical products, plant extracts, homeopathic substances, vitamins, or other compounds into subcutaneous fat) have been involved in the transmission of rapidly growing mycobacteria (1, 24, 42, 117). The clinical manifestations of cutaneous involvement include

TABLE 4 Risk factors for acquiring major nontuberculous mycobacterial infections of the skin and soft tissues and medical and surgical recommendation

Mycobacterial species	Risk factors for cutaneous disease	Therapy
M. fortuitum	Dermal piercing, tattoos, mesotherapy, acupuncture, intravascular devices (e.g., central venous catheters), peritoneal dialysis catheters	Combination of macrolide, fluoroquinolones, doxycycline, trimethoprim-sulfamethoxazole; surgical excision may be indicated
M. abscessus complex	Cosmetic surgery, postsurgical infections, acupuncture, mesotherapy, pedicure sessions	Combination of macrolide (azithromycin or clarithromycin), cefoxitin, imipenem, amikacin; surgical excision and/or debridement need to be considered for severe deep tissue involvement
M. chelonae	Tattoos, mesotherapy, acupuncture	Combination of macrolide (azithromycin or clarithromycin), cefoxitin, imipenem, fluoroquinolones, amikacin; surgical excision may be indicated
M. haemophilum	Cosmetic procedures, permanent makeup, HIV infection/AIDS, anti-TNF-α blockers, freshwater or salt water injuries	Combination of macrolide (clarithromycin), fluoroquinolones, rifamycin; surgical excision may be indicated, similarly to infections caused by *M. abscessus* complex
M. marinum	Freshwater or salt water injuries associated with fishing injuries, coral trauma, and other related injuries	Combination of clarithromycin and ethambutol or trimethoprim-sulfamethoxazole and rifampin; alternative drugs include doxycycline or minocycline
M. kansasii	HIV infection/AIDS, renal transplant, chronic pulmonary diseases	Combination of isoniazid, rifampin, ethambutol; clarithromycin may be used instead of isoniazid; linezolid is an alternative drug

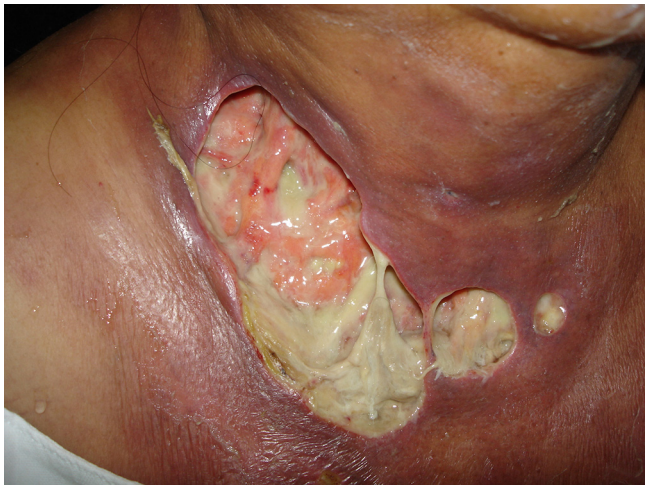

FIG 6 An adult with *Mycobacterium abscessus* infection presenting as scrofuloderma with extensive tissue destruction in the right cervical and supraclavicular areas.

cellulitis, papular lesions, nodules with purple discoloration, abscesses, draining sinuses, subcutaneous nodules (pseudoerythema nodosum), and ulcerations (117). Some individuals may manifest with a single lesion, but others manifest with multiple lesions, depending on the mode of acquisition and level of host immunity (42, 117). NTM infections of the skin may spread to cause tenosynovitis, myositis, osteomyelitis, and septic arthritis (24, 42, 117).

Mycobacterium abscessus was first identified in a patient with a knee infection and subcutaneous abscesses in 1950 (117). Among the rapidly growing mycobacteria, it is the most common cause of lung disease (117). Along with *Mycobacterium fortuitum* and *Mycobacterium chelonae*, members of the *M. abscessus* complex (*M. abscessus*, *Mycobacterium massiliense*, and *Mycobacterium bolletii*) are the major NTM associated with cutaneous involvement (Fig. 6) (1, 24, 42, 117). Localized cutaneous infections are due to posttraumatic wound infection, catheter-associated infections (e.g., from peritoneal dialysis or central venous catheters), postsurgical infections, and trauma-associated infections (Fig. 7) (24, 42, 117). *M. chelonae* and *M. abscessus* usually present with multiple skin lesions, while *M. fortuitum* tends to present as a single lesion (24, 42, 43, 117). Susceptibilities to antimicrobials depend on the species. Members of the *M. abscessus* complex tend to be susceptible to macrolides, amikacin, cefoxitin, and

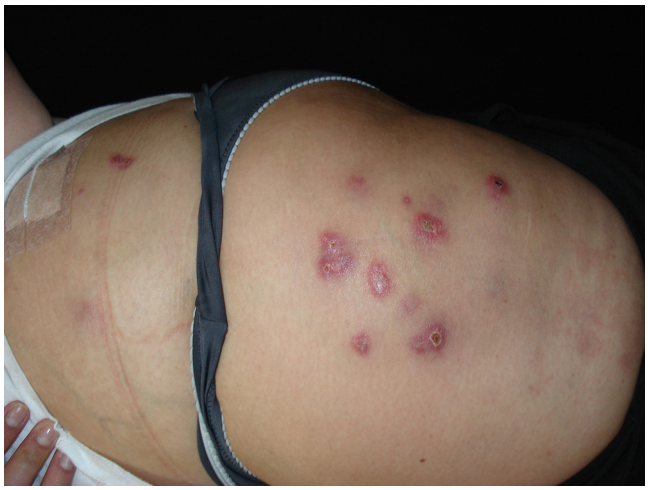

FIG 7 Infection caused by *Mycobacterium fortuitum* associated with mesotherapy.

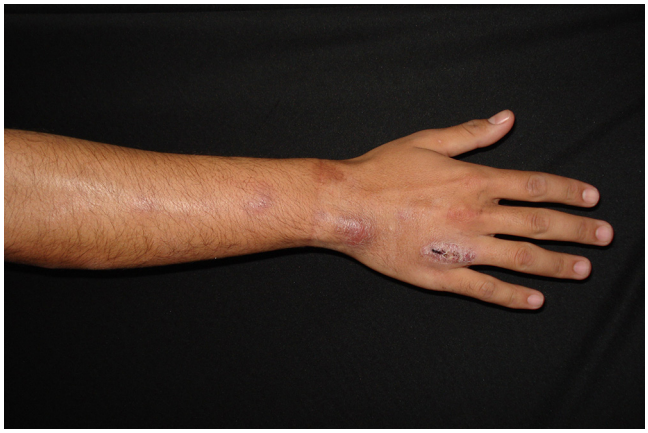

FIG 8 Characteristic sporotrichoid nodular lymphangitic spread of *Mycobacterium marinum*.

imipenem (115). However, it is important to confirm the detection of inducible macrolide (clarithromycin) resistance by the presence of the *erm41* gene (1, 117, 118). Detection of *in vivo* resistance to macrolides requires incubation of NTM isolates with clarithromycin prior to determining an MIC (117, 118). Azithromycin is the preferred agent in *M. abscessus* infections, whereas clarithromycin or azithromycin is effective in cases of *M. massiliense* (117, 118). *M. fortuitum*, *M. abscessus*, and *M. chelonae* are resistant to all of the antituberculosis agents (1, 24, 42, 115). *M. fortuitum* is susceptible to macrolides, amikacin, doxycycline, fluoroquinolones, and trimethoprim-sulfamethoxazole. Finally, *M. chelonae* is often susceptible to macrolides, cefoxitin, fluoroquinolones, and tobramycin (1, 42).

Mycobacterium kansasii

M. kansasii was identified in 1953 as causing an infectious disease that produces lung cavitary lesions resembling those in pulmonary TB (119). *M. kansasii* has been identified only in municipal water systems (21, 22, 42). *M. kansasii* infection manifests predominantly as pulmonary disease. Cutaneous involvement of *M. kansasii* is usually present in immunocompromised hosts and sometimes with concomitant pulmonary disease or disseminated disease (24, 37). Cutaneous infection may present as nodules, pustules, verrucous lesions, erythematous plaques, ulcers, and abscesses (Fig. 8). It may also be associated with osteomyelitis and septic arthritis. This infection may occur among immunocompetent and immunocompromised hosts, including those with HIV infection/AIDS or with renal transplantation. Similarly to *M. tuberculosis*, *M. kansasii* expresses ESAT-6 and CFP-10 analogs, and therefore IFN-γ release assays (IGRAs) are not useful in distinguishing this infection from *M. tuberculosis* infection (37). *M. kansasii* is susceptible to isoniazid, rifampin, ethambutol, clarithromycin, fluoroquinolones, and aminoglycosides but is intrinsically resistant to pyrazinamide (37, 119). Susceptibility testing is recommended only for rifampin given the fact that the best clinical outcomes are associated with rifampin susceptibility (37, 119).

Mycobacterium haemophilum

M. haemophilum requires iron or hemin supplementation for growth (35, 36, 42, 119). *M. haemophilum* was identified in 1978 in individuals with skin infections. *M. leprae* and *M. haemophilum* have important similarities, including the presence of large quantities of docosanoic acid, and *M. haemophilum* possesses a phenolic glycolipid antigen analogous to the one expressed by *M. leprae*. Furthermore, *M. leprae* and *M. haemophilum* are phylogenetically related and also share ancestry with other mycobacterial species, such as *M. marinum* and *M. ulcerans* (35, 36, 119). Patients with *M. haemophilum* may also experience immune reconstitution events analogous to leprosy reactions or to paradoxical immune reactions seen after initiating antimycobacterial

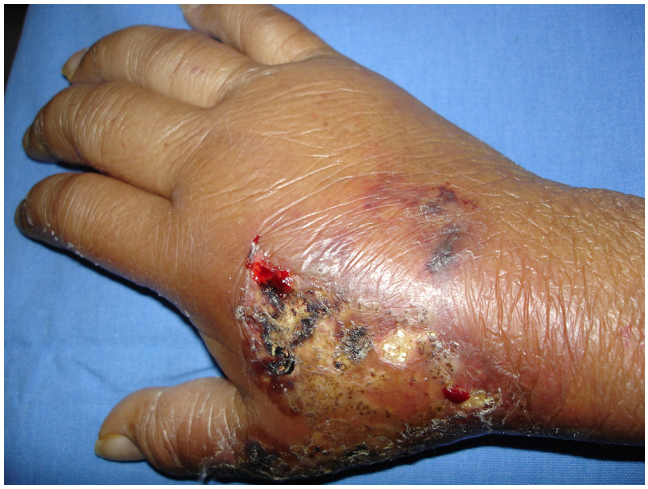

FIG 9 Severe hand swelling and nodular lymphangitic lesions caused by *Mycobacterium marinum* infection.

therapy in patients with *M. tuberculosis* infection (35, 36, 119). This infection may present as a localized or disseminated disease in immunocompromised hosts, including those with HIV infection/AIDS, transplant recipients, and those receiving biological agents such as anti-TNF-α agents (119). This organism preferentially grows at 30°C, explaining its predilection for causing lesions in the upper and lower extremities (34–36). However, *M. haemophilum* has been associated with subcutaneous infections, lymphadenitis, septic arthritis, osteomyelitis, pneumonitis, and disseminated disease. Like disease caused by *M. marinum* or *M. ulcerans*, the cutaneous disease caused by *M. haemophilum* may present after salt water injuries (24, 36).

The clinical spectrum of cutaneous manifestations of *M. haemophilum* includes multiple skin lesions presenting as erythematous or violaceous papules, plaques, or nodules. Some of these lesions evolve into necrotic abscesses or deep-seated ulcerations (36). Most of these presentations occur in the extremities, particularly over joints. Earlier lesions presenting as papules or nodules are usually painless but when these lesions evolve into ulcerations or abscesses, patients may experience significant pain. In children, this infection usually presents as cervical lymphadenitis (35, 36). Treatment involves a combination of clarithromycin, ciprofloxacin, and rifampin or rifabutin for 12 to 24 months (34–36, 42).

Mycobacterium marinum

M. marinum is a slowly growing pigmented organism responsible for "fish tank granuloma" due to its ability to cause localized skin and soft tissue infections in individuals with exposure to contaminated freshwater or salt water (24, 42, 120). Disease caused by *M. marinum* is associated with minor to moderate skin infections presenting as granulomatous lesions similar to those caused by *M. tuberculosis or M. haemophilum*. Most cases of cutaneous infections take place among individuals who suffered puncture injuries or other types of trauma in freshwater or salt water. The clinical spectrum of cutaneous disease caused by *M. marinum* includes a solitary papule or nodule that may ulcerate and then spreads in a sporotrichoid pattern (lymphangitic spread) (Fig. 9) (120). Because its optimal temperature for growth is around 30°C, cutaneous lesions most frequently occur in the upper or lower extremities and sometimes in the tip of the nose. *M. marinum* may produce deep tissue involvement (Fig. 10) or disseminated disease among severely immunocompromised hosts (120). Treatment of this mycobacterial infection requires a combination of at least two drugs, including a macrolide, ethambutol, trimethoprim-sulfamethoxazole, or rifamycin, with a duration of therapy ranging from two to six months depending on the degree of cutaneous involvement (24, 42, 120).

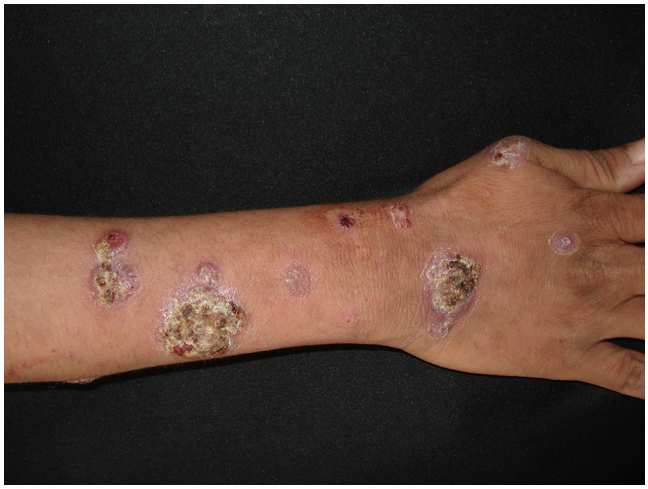

FIG 10 *Mycobacterium kansasii* leading to a sporotrichoid nodular lymphangitis of the right arm.

Mycobacterium avium-intracellulare

Cutaneous involvement of *M. avium-intracellulare* complex (MAC) infections has been rarely reported (121–125). MAC is composed of several different slowly growing mycobacterial species, including *M. avium*, *M. intracellulare*, *Mycobacterium indicus pranii*, *Mycobacterium chimera*, *Mycobacterium arosiense*, and many others. The spectrum of clinical manifestations includes papular, nodular lesions with a sporotrichoid pattern, verrucous ulcers, inflammatory pseudotumors, draining sinuses, and cold abscesses (Fig. 11) (121–125). Modes of acquisition of MAC infection include trauma, cosmetic procedures (such as pedicures, footbaths, and leg waxing), and postsurgical infections (126). Recent outbreaks of severe, life-threatening infections caused by *M. chimera* were associated with extracorporeal circulation following cardiothoracic surgery procedures. Many of these patients presented with surgical wound infections (41, 116, 125).

DIAGNOSIS OF CUTANEOUS MYCOBACTERIAL INFECTIONS

The diagnosis of mycobacterial infections of the skin and soft tissues requires a low threshold of clinical suspicion given the broad spectrum of potential clinical presentations. Confirming a diagnosis of cutaneous mycobacterial infections requires tissue biopsies of cutaneous lesions to assess for the presence of acid-fast bacilli and cultures of tissue specimens or material obtained from draining lesions (1, 42). Some mycobacterial species have specific growth requirements in solid or liquid culture media. Molecular techniques such as 16S rRNA gene sequencing, PCR analysis, and high-

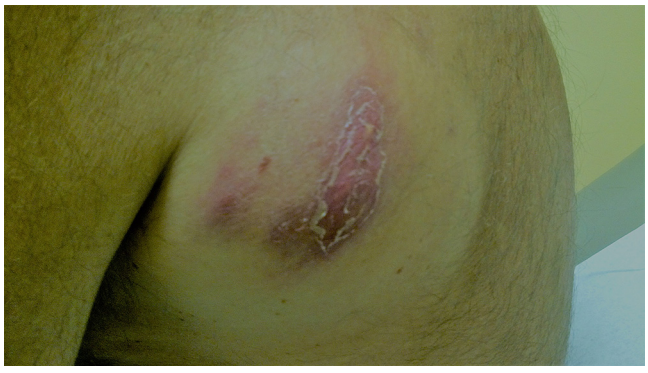

FIG 11 Cold abscess caused by *Mycobacterium avium-intracellulare* complex infection in a 60-year-old male.

performance liquid chromatography are methods that improve the ability to identify mycobacterial pathogens in tissue specimens.

The clinical diagnosis of leprosy relies on the identification of characteristic plaques, macules, or nodules concomitantly with sensory loss in the form of hypoesthesia or anesthesia and the presence of thickened nerves (72, 74). Tissue biopsies of lesions may demonstrate, using Fite-Faraco staining, the presence of acid-fast bacilli residing inside nerves and perineural or intraneural granulomas (47). In addition, histopathological evaluation of tissue samples contributes to defining the immunopathological spectrum of polar and borderline forms of leprosy (47). The identification of Buruli ulcer often relies on the presence of characteristic nodules or ulcers, ecological risk factors, and at-risk age groups residing in settings of endemicity. Culturing *M. ulcerans* is cumbersome since it requires a low oxygen concentration and a temperature between 29°C and 33°C. Molecular identification of *M. ulcerans* by employing quantitative PCR (qPCR) assays is an alternative methodology for confirming a diagnosis of Buruli ulcer. The use of point-of-care diagnosis of Buruli ulcer is under evaluation in field studies in settings of endemicity (1, 42). Identifying *M. tuberculosis* in tissue specimens through culture or molecular detection is of paramount significance when suspecting most clinical forms of cutaneous tuberculosis.

Treatment guidelines recommend performing susceptibility testing of mycobacterial isolates with the goal of optimizing the choice of specific antimycobacterial drug combinations, since the MIC to specific antimicrobials correlates clinically with *in vivo* responses to antimicrobial therapy for many mycobacterial species (1, 42). It is recommended that rapidly growing mycobacteria be tested against selected antibacterial drugs of different classes (1, 42). Susceptibility testing for *M. leprae* involves assessments of specific genetic markers of antimycobacterial resistance (99).

CONCLUSIONS

The most common clinical presentations of mycobacterial infections include pulmonary, cutaneous and disseminated forms in immunocompromised hosts. Cutaneous mycobacterial infections may manifest with localized or diffuse lesions. Disruption of skin and soft tissues frequently constitutes the portal of entry of NTM from environmental niches (soil, natural water systems, engineered water networks, etc.) (21, 22). In addition, some mycobacterial infections affecting cutaneous structures occur after exposures to infected animals or their products (127, 128). The most frequently identified mycobacterial pathogens involving the skin and soft tissues include *Mycobacterium leprae Mycobacterium ulcerans* and *M. tuberculosis*. However, NTM are becoming important emerging pathogens in different geographical areas. Of these, rapidly growing mycobacteria, *M. haemophilum*, and *M. marinum* are important agents involving cutaneous structures. Further clinical and epidemiological research that advances our understanding of mycobacterial pathogens that infect the skin and soft tissues may improve our ability to prevent these infections and optimize their medical management.

ACKNOWLEDGMENT

We have no conflicts of interest to disclose.

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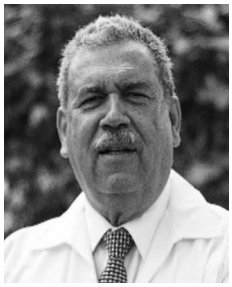

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